Commentary

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Toxic Wastes and Kidney Disease: Research Needs

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In 1981 over one billion dollars will be spent sustaining the lives of patients with end-stage renal disease by hemodialysis and renal transplantation, but less than 0.02% of this amount will be invested in studies of nephrotoxicity (*1*). Any knowledge of the effect of industrial waste on human kidney disease gained from this miniscule effort will probably be serendipitous. Our monumental ignorance of this subject appears to have two sources. First, research on nephrotoxicity is largely confined to acute, high-dose exposure in animals; the delayed effects of chronic low-dose exposure in man remain virtually unexplored. Second, the etiology of most chronic kidney diseases in man is unknown. The diagnostic categories commonly used for end-stage renal diseases rarely stipulate underlying causes.

Roughly 60% of dialysis and transplant patients are reported to have glomerulonephritis or interstitial nephritis. These two entities encompass most acquired chronic renal diseases. Yet methods for determining etiology are rudimentary, arbitrary or applicable only in a few highly specialized research laboratories. In addition, the standard clinical techniques for detecting renal disease, irrespective of etiology, have been improved little in sensitivity or specificity since they were described by Richard Bright 150 years ago. Chronic glomerulonephritis is usually detected by the presence of albuminuria, while renal failure is detected by elevations of the blood urea nitrogen (BUN) or serum creatinine (Scr). Unfortunately, proteinuria is characteristically absent in the early phases of interstitial nephritis and azotemia is not apparent until more than two-thirds of kidney function is lost. Consequently, toxin-induced chronic interstitial nephritis which is characterized in its early phases by the absence of albuminuria cannot usually be detected until the disease has become advanced. As the end stage is approached, etiologic differentiation is confounded by the long interval between renal insult and clinical manifestations. The final common pathway of renal disease is similar regardless of the underlying cause. The problems of early detection of renal dysfunction and the determination of etiology must be resolved before progress can be expected in unraveling the impact of environmental toxins on the kidneys.

The list of substances known to be toxic to the kidneys is enormous. It is also incomplete and provides only a very crude guide for evaluating the chronic renal effects of toxic wastes. Virtually any substance introduced into the body in sufficient quantities will produce acute renal failure. It should be remembered that the kidney receives almost one quarter of the cardiac output. In performing its major functions of controlling salt and water balance and eliminating biological wastes while conserving essential constituents of blood, the kidney concentrates toxic materials in its cells and intratubular fluid. In addition, the kidney metabolizes many toxic substances sometimes producing toxic degradation products. Because the concentrations of toxins may be several hundred times greater in the kidney than elsewhere, blood concentrations which are harmless to other tissues may herald renal damage.

Epidemiologic studies limited to the measurement of Scr and urinary protein are not likely to provide compelling information on the role of specific nephrotoxins in renal disease. In-depth, long-term studies of more subtle renal dysfunction will surely be required for this purpose. Fundamental to such studies is the quantitation of glomerular filtration rate (GFR) using clearance techniques. Short cuts for assessing GFR by the use of the serum creatinine, endogenous creatinine clearance or single dose blood disappearance curves sacrifice accuracy for convenience and may be misleading. Many

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nephrotoxins produce relatively specific defects in renal tubular transport functions which, however, may be present only transiently in the course of exposure. Such tubular defects must be studied by cumbersome physiologic techniques if characteristic patterns are to be identified. Examples of such renal dysfunctions are the aminoaciduria in childhood lead poisoning, β_2-microglobulin excretion in cadmium nephropathy and renal tubular acidosis in toluene poisoning.

Studies will have to be undertaken in the early stages of disease and followed over many years if cause and effect relationships are to be established with confidence. Once azotemia supervenes, the problem of identifying appropriate control subjects becomes particularly challenging. Compilation of data on control renal failure subjects in whom prior exposure and etiology of renal disease is unknown is unlikely to illuminate the problem. Control data must be collected with the same meticulous approach used in the study of specific disease entities. If characteristic nephrotoxic effects of individual toxins are to be identified, functional data will have to be corrected for such factors as the state of hydration, glomerular filtration rate, proteinuria and osmotic clearance. A lesser undertaking will be unconvincing because useful data will have been discarded. There are no quick solutions in sight for understanding the pathophysiology and pathogenesis of kidney disease.

Animal models are essential for the full elucidation of toxic nephropathy. Their interpolation in terms of human disease is, however, frought with difficulties. After decades of intensive study of normal renal function, renal physiologists have begun to attack the problem of acute high-dose nephrotoxicity. The time is now ripe for gaining insight into chronic, low-dose nephrotoxicity but for this purpose research grants longer than five years duration will have to be awarded.

Assessment of past toxic exposure is at least as difficult as determining the etiology of renal disease. The outlook for determining body content of industrial wastes is brightened by the potential application of modern physics technology to the detection of trace metals and of modern chemical technology for measuring organic compounds. Blood and urine measurements have been the mainstay of clinical chemistry for two centuries. Despite long tradition and great convenience, such measurements appear to be of limited value in the assessment of cumulative exposure for many substances with toxic potential. On the other hand, X-ray-induced fluorescence for detection of bone lead stores and neutron activation analysis for detection of renal cadmium content appear ready for exploitation. The importance of photon and particle accelerators for the measurement of trace elements in tissue specimens *in vitro* as well as *in vivo* cannot be overestimated (*2*). Electron microscopy may well take on the musty aura of traditional anatomy as advanced particle accelerators define the elemental composition of intracellular organelles. Trace metal measurements at the whole body and subcellular level provide some of the most promising prospects for understanding the effects of waste products on the kidney in the near future. Nuclear magnetic resonance, chromatography combined with mass spectroscopy and selective tissue electrodes are just coming into their own as tools for biological research.

For many toxic substances, however, practical assessment of past exposure may not be feasible by direct measurement. A threshold effect may prove elusive if cellular damage is cumulative, but the toxin is not retained. When appropriate tissue samples are inaccessible or when the offending agent is no longer present, biologic evidence of past exposure must sometimes be obtained by indirect measurements of metabolic consequences. An example of a biologic consequence of toxicity which may be useful for detecting toxin exposure is 6-β-hydroxycortisol excretion. This adrenocortical metabolite has been reported to be increased following dioxan exposure and decreased following lead exposure. Such indirect approaches may be particularly important for identifying the biologic consequences of vast numbers of organic chemicals produced by industry. Nevertheless, immediate prospects for establishing etiologic significance of organic pollutants including pesticides are less promising than are the prospects for establishing heavy metal toxicity.

Since many of the foregoing generalizations arise from my personal experience with lead nephropathy over the past decade, it may be worthwhile to review some of the specific lessons. For purposes of this discussion I will not reiterate the clinical data we have collected or try to persuade you of the validity of our conclusions. Rather, I will ask you to suspend disbelief for a moment, accept our conclusions and contemplate how such clinical observations might have been overlooked for so long a time. Very briefly, our studies show that lead nephropathy is common among asymptomatic workers occupationally exposed to lead (*3*). Furthermore, lead appears to contribute to the renal disease encountered in gout patients and usually termed "gouty nephropathy" (*4*). Finally, our studies suggest that lead may explain the occurrence of renal failure in many hypertensive patients usually thought to have "essential" hypertension (*5*). These

conclusions were derived primarily from the EDTA ($CaNa_2$ edetate) lead mobilization test. Mobilizable lead was increased in the vast majority of asymptomatic lead workers, as well as in persons with gout and hypertensive patients with renal failure. This provocative chelation test made diagnosis possible. None of our patients had overt symptoms of lead intoxication, none had elevated blood or urine lead concentrations by prevalent standards and heme synthesis measurements fell within normal limits at the time of clinical examination. Unlike the gout and hypertensive patients, the men with occupational lead nephropathy had no clinical evidence of renal disease such as proteinuria or azotemia. Reductions of 30-50% in GFR were found in these lead workers by measurement of ^{125}I-iothalamate clearance, a lengthy research laboratory procedure. The restoration of renal function towards normal by long-term low-dose EDTA therapy in four of eight lead workers confirmed the etiologic diagnosis and attested to the efficacy and safety of the EDTA treatment.

The relevant lessons from these studies are, I think, as follows: (1) textbook descriptions of chronic poisoning do not provide criteria for the diagnosis of subclinical toxicity; (2) blood and urine measurements are often inadequate for assessment of chronic exposure; (3) prevention and treatment cannot be instituted until pathogenesis is understood. Finally, early nonglomerular renal disease cannot be found by measuring proteinuria and serum creatinine. There is another lesson which, I am afraid, is of considerable relevance to a symposium on research needs: apart from the Veterans Administration Research Service, no other federal agency would support this work nor would any one of several private foundations. Review committees from the NIH, NIOSH, EPA and NSF have repeatedly rejected proposals for lead studies prepared from a variety of points of view by a variety of investigators. Not only is the funding bureaucracy (of which I am a sometimes member) unwilling to take risks, but they are reluctant or unable to cross traditional research lines.

It may be noteworthy that despite the Veterans Administration's support of lead nephropathy studies over the past two decades, the VA has received little recognition for its contributions in this field. A recent National Academy of Science report on government sponsored lead research identifies the Veterans Administration among those agencies not engaged in significant research in lead. I am inclined to agree with Clair Pattersons's minority opinion included in the NAS report (*6*), which can be paraphrased as follows: it is precisely the obscurity of the VA endeavor that has permitted this agency to support research that does not simply confirm preexisting concepts.

Despite the limited resources devoted to understanding the effect of environmental toxins on the kidney, some promising insights have been gained in the last decade. Surprising interactions between metals (*7*) and between organic compounds and metals (*8*) have been found when experiments were designed to elucidate such complexities. It has recently been shown that certain organic pollutants sensitize the kidney to the toxic effects of other organic compounds. Kluwe and Hook (*9*) at the NIEHS have made major strides in clarifying the nephrotoxic interactions of several organic compounds in animal models. They have recently demonstrated in rats, for example, that increased renal susceptibility to toxins is transmitted to pups in maternal milk by dams fed polybrominated biphenyls (*10*).

The study of the effects of toxic wastes is necessarily multidisciplinary. The glomerulonephritis and interstitial nephritis induced by chronic low-dose exposure to toxic agents may be immunologically mediated. Epidemiologic studies have provided suggestive evidence that solvent fumes increase susceptibility to the development of glomerulonephritis in man (*11*). Although these conclusions are based entirely on historical information recalled by patients, the hypothesis warrants careful prospective evaluation in the industrial setting and animal research laboratory. Immunologic mediation has been more clearly demonstrated in studies of mercury-induced glomerulonephritis in rats by Druet and his associates in France (*12*). Their work suggests that mercuric chloride elicits glomerular immune disease by effects on immunocompetent lymphocytes rather than by modification of endogenous antigens. Glomerular disease due to mercury may therefore be unrelated to the mercury content of the kidney in contrast to acute tubular necrosis which is dependent on cellular accumulation of the toxic metal. This rat model may have important implications for the pathogenesis of mercury-induced proteinuria in man. The sporadic appearance of nephrotic syndrome induced by environmental toxins will not, however, meet Koch's postulates until our knowledge of immunogenetics is greatly refined.

The answers to most questions about environmental nephrotoxins are dependent upon advances in basic biology and technology. Crucial stepping stones will, in my opinion, come from studies of membrane structure and function, immunology, genetics, metabolism and cell biology. While awaiting these developments we must exploit available techniques of renal physiology and applied physics.

Concensus is appropriate for political decision-making when inadequate information is available, but public confidence in the face of ignorance is fragile. In some ways, the media handling of toxic waste issues reminds me of the medieval response to plague and leprosy—in the absence of the necessary facts, the public's energy is directed towards exorcising the devil. Sound information is a constructive way to dissipate fear of an environment that is perceived to be out of control. Such information will not be easy or inexpensive to acquire. Economic constraints demand that the effort be highly selective. Research at its best is opportunistic—effort must be placed in those areas which current technology and knowledge have ripened for fruitful investigation. The questions to attack are not just those that are of most public concern but those that contemporary methodology can resolve. We are likely to be overwhelmed with the expense of such "intermediate technologies" as dialysis and transplantation until we are willing to invest sufficient resources in research to make preventive nephrology a reality.

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